

MOLECULAR PATHOGENESIS AND NEW INTERVENTIONS IN SCLERODERMA

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RFA: AR-00-007

National Institute of Arthritis and Musculoskeletal and Skin Diseases
Office of Research of Women's Health

Letter of Intent Receipt Date: October 1, 2000

Application Receipt Date: December 15, 2000

THIS RFA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS RFA.

PURPOSE

The goal of this Request for Applications (RFA) is to foster developmental and traditional research projects to advance our understanding of the pathogenesis of scleroderma and to promote the design, development and pilot testing of hypothesis-driven innovative therapeutic approaches. Systemic sclerosis (scleroderma) is a chronic condition characterized by the progressive thickening of the skin and involvement of internal organs, most notably the heart, kidneys, lungs and digestive tract. This RFA is based in part on the scientific opportunities identified in the conference "Emerging Opportunities in Scleroderma Research". A summary of the conference and research questions raised can be found at <http://www.nih.gov/niams/reports/sclersum.htm>.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010", a PHS-led national activity for setting priority areas. This RFA is related to several objectives, particularly those listed in the chapter "Arthritis, Osteoporosis, and Chronic Back Conditions". Potential applicants may obtain "Healthy People 2010" at <http://www.health.gov/healthypeople>.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic for-profit and non-profit organizations, public or private, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the Federal government. Foreign institutions are not eligible to apply for these grants, however, applicants may collaborate, through consultation or contractual agreements, with investigators at foreign institutions. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

MECHANISM OF SUPPORT

The mechanisms of support will include the investigator-initiated research project grant (R01) and the exploratory/developmental research grant (R21).

R21 Applications. Use of this mechanism is recommended for investigators experienced in scleroderma research who wish to adapt new methods or techniques established in other fields to develop scientific approaches and models to study the pathogenesis and gather pre-clinical data of new therapies or preliminary data on toxicity and potential efficacy in a limited number of patients. Investigators with expertise in fields other than scleroderma who wish to establish new research programs on the disease are also encouraged to use this mechanism.

Exploratory/developmental studies are not intended for large scale undertakings, nor to support or supplement ongoing research. Instead, investigators are encouraged to explore the feasibility of an innovative research question or approach which may not be justifiable through existing research to compete as a standard research project grant (e.g., R01), and to develop a research basis for a subsequent application through other mechanisms, i.e., R01, P01. If desired, the specific aims of the R21 project may be incorporated into a research project grant application (R01) submitted prior to the termination of the R21 award.

Investigators proposing to conduct small, pilot/toxicity clinical trials are advised to review the NIAMS guidelines for preparation of clinical trial applications and the NIAMS guidelines for Data and Safety Monitoring Boards (<http://www.nih.gov/niams>).

Investigators who wish to establish new collaborative research programs with intramural laboratories at the NIAMS, and apply for funding under this RFA, are encouraged to contact Dr. Barbara Mittleman, Director of Scientific Interchange, NIAMS (mittlemb@mail.nih.gov).

Because the nature and scope of the research proposed in response to this RFA may vary, it is anticipated that the size of an award will vary also. Modular budgeting procedures apply for grants up to \$250,000. Specific R01 application instructions have been modified to reflect "Modular grant" and "Just-in-time" streamlining efforts. Complete instructions and information on Modular Grants can be found at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

FUNDS AVAILABLE

It is anticipated that for FY 2001 approximately \$1.5 million total costs will be available for the first year of support for this initiative. Award of grants is contingent upon the receipt of such funds for this purpose. The specific number to be funded will depend on the merit and scope of the applications received and the availability of funds. Applicants may request up to five years of support for the R01. Direct costs will be awarded in modules of \$25,000, less any overlap or other necessary administrative adjustments. Facilities and Administrative costs will be awarded based on the negotiated rates.

Exploratory/developmental (R21) grants, may not exceed \$75,000 per year in direct costs, including indirect costs for collaborating institutions, if any. The total project period for an R21 application submitted in response to this RFA may not exceed three years. These grants are non-renewable and continuation of projects developed under the R21 program will be through the traditional unsolicited (R01 or P01) grant programs.

RESEARCH OBJECTIVES

The pathogenesis of scleroderma is complex and not well understood. Immune activation, vascular abnormalities and dysregulation of extracellular matrix components contribute to end stage obliterative vasculopathy and fibrosis. Host and environmental factors may contribute to disease predisposition and onset. Although these disease components have been known for some time, their roles in disease initiation and progression are unclear. Research efforts in scleroderma have been focused on the analysis of the immune abnormalities with emphasis on the molecular characterization of autoantibodies specificity, and more recently on autoreactive T cells and cytokine production. Another major research focus has been on the analysis of abnormal collagen production and the regulatory molecular pathways that control collagen production by fibroblasts. Recently, however, new clues point to host factors related to immune activation and regulation of endothelial cell activity as potentially key early events in the pathogenesis of scleroderma.

A group of scleroderma researchers and experts in other relevant fields was convened in December of 1997 to explore the new and emerging research findings in scleroderma, identify research gaps and opportunities and foster research collaborations. A summary of the conference and research questions raised can be found at <http://www.nih.gov/niams/reports/sclersum.htm>.

The purpose of this announcement is to encourage pilot and developmental projects (R21) and investigator initiated research projects (R01) that explore new approaches and hypotheses on the pathogenesis of scleroderma. In addition, the initiative also seeks to promote the development and pilot testing of new therapeutic approaches, including alternative and complementary medicine. Potential areas of research include, but are not limited to:

- o the role of apoptosis-related molecules and other intracellular events in fibroblasts, immune and endothelial cells in scleroderma;

- o the role and regulation of oxygen radicals and other mediators of local tissue injury in skin and other organ involvement;

- o the role of microchimerism in the induction of local tissue changes, and systemic and local immune dysregulation;

- o the study of genes that may contribute to disease onset or manifestations;

- o studies on the regulation of synthesis, structure, function and clearance of molecular components of the extracellular matrix (ECM);

- o analysis of interactions between ECM and immune cells;

- o the study of molecular and cellular events in the vascular wall that contribute to reactivity and vasculopathy;

- o mechanisms of induction of injury and repair of organs involved in the disease;

- o therapies that control ECM metabolism;

- o pharmacologic and alternative approaches leading to reduction of GI symptoms and tissue injury;

- o new approaches to reduce progressive lung disease;
- o new animal model systems to dissect disease pathogenesis and test new therapies;
- o studies designed to explore the molecular and/or genetic basis for sex, gender and ethnic disparities; and
- o clinical research studies on biomarkers and new diagnostic methodologies.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000

(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>);

a complete copy of the updated Guidelines are available at

http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm: The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications

submitted for receipt dated after October 1, 1998. All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: <http://grants.nih.gov/grants/guide/notice-files/not98-024.html>.

Investigators may also obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES

All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

LETTER OF INTENT

Prospective applicants are asked to submit, by October 1, 2000, a letter of intent that includes a descriptive title of the proposed research; the name, address, and telephone number of the Principal Investigator; the identities of other key personnel and participating institutions; and the number and title of this RFA. Although a letter of intent is not required, is not binding, does not commit the sender to submit an application, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and avoid conflict of interest in the review. The letter of intent is to be sent (e-mail, fax or post) to Dr. Tommy Broadwater at the address listed under INQUIRIES.

APPLICATION PROCEDURES

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and Institute staff. The Research Grant Application Form PHS 398 (rev. 4/98), with the modifications noted below, is to be used in applying for these grants.

BUDGET INSTRUCTIONS

Modular Grant applications will request direct costs in \$25,000 modules, up to a total direct cost request of \$250,000 per year. Applications that request more than \$250,000 direct costs in any year must follow the traditional PHS 398 application instructions. The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

FACE PAGE - Items 7a and 7b should be completed, indicating Direct Costs (in \$25,000 increments up to a maximum of \$250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period, and Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

NARRATIVE BUDGET JUSTIFICATION - Prepare a Modular Grant Budget Narrative page. (See <http://grants.nih.gov/grants/funding/modular/modular.htm> for sample pages.) At the top of the page, enter the total direct costs requested for each year. This is not a Form page.

Under Personnel, list all project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest \$1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of key personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is

included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium.

Provide an additional narrative budget justification for any variation in the number of modules requested.

BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at <http://grants.nih.gov/grants/funding/modular/modular.htm>.

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years; and
- List selected peer-reviewed publications, with full citations.

RESEARCH PLAN B The research plan (a-d) is limited to 20 pages for R01s and 10 pages for R21 applications. Applications that exceed the page limit will be returned without review. An appendix may be included in the application, however, the appendix is not to be used to circumvent the page limit of the research plan.

CHECKLIST - This page should be completed and submitted with the application. If the facilities and administration (F&A) rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

Applications are to be submitted on the Grant Application Form PHS 398 (rev. 4/98). These forms are available at most institutional offices of sponsored research; from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: grantsinfo@nih.gov; and on the internet at <http://grants.nih.gov/grants/funding/phs398/phs398.html>.

For purposes of identification and processing, item 2a on the face page of the application must be marked "YES" and the RFA number "AR-00-007" and the words "MOLECULAR ATHOGENESIS AND NEW INTERVENTIONS IN SCLERODERMA" must be entered on the face page.

The RFA label and line 2 of the application should both indicate the RFA number. The RFA label must be affixed to the bottom of the face page. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review.

The sample RFA label available at <http://grants.nih.gov/grants/funding/phs398/label-bk.pdf> has been modified to allow for this change. Please note this is in pdf format.

Applications must be received by December 15, 2000. Applications not received as a single package on the receipt date or not conforming to the instructions contained in PHS 398 (rev. 4/98) Application Kit (as modified in, and superseded by, the special instructions below, for the purposes of this RFA), will be judged non-responsive and returned to the applicant.

If the application submitted in response to this RFA is substantially similar to a grant application already submitted to the NIH for review, but that has not yet been reviewed, the applicant will be asked to withdraw either the pending application or the new one. Simultaneous submission of identical applications will not be allowed, nor will essentially identical applications be reviewed by different review committees. Therefore, an application that is essentially identical to one that has already been reviewed cannot be submitted in response to this RFA. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

An application in response to this RFA may be of interest to the National Heart, Lung, and Blood Institute (NHLBI) and possible assignment to that Institute will be considered on a case-by-case basis depending on the objectives of the study.

Submit a signed, typewritten original of the application, including the checklist, and three signed, exact, single-sided photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040 - MSC 7710
Bethesda, MD 20892-7710

Bethesda, MD 20817 (for express mail or courier service)

At the time of submission, two additional exact copies of the grant application and all five sets of any appendix material must be sent to Dr. Tommy Broadwater at the address listed under INQUIRIES.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the NIH National Center for Research Resources may wish to identify the GCRC as a resource for conducting the proposed research. If so, a letter of agreement from either the GCRC Program Director or Principal Investigator should be included with the application.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the NIH Center for Scientific Review and for responsiveness by NIAMS staff; those judged to be incomplete or not in the format specified in this RFA will be returned to the applicant without review. Those considered to be non-responsive will be returned without review.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by NIAMS in accordance with the review criteria stated below. As part of the initial merit review, a process will be used by the initial review group in which all applications will receive a written critique but only those applications deemed to have the highest scientific merit will be discussed, assigned a priority score, and receive a second level review by the National Arthritis and Musculoskeletal and Skin Diseases Advisory Council.

REVIEW CRITERIA

The five criteria to be used in the evaluation of grant applications are listed below. To put those criteria in context, the following information is contained in instructions to the peer reviewers.

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. The reviewers will comment on the following aspects of the application in their written critiques in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered by the reviewers in assigning the overall score weighting them as appropriate for each application. Note that the application does not need to be

strong in all categories to be judged likely to have a major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

2. Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

4. Investigator. Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

- o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

- o The reasonableness of the proposed budget and duration in relation to the proposed research

- o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application

The personnel category will be reviewed for appropriate staffing based on the requested percent of effort. The direct costs budget request will be reviewed for consistency with the proposed methods and specific aims. For modular grant applications, any budgetary adjustments recommended by the reviewers will be in \$25,000 modules. The duration of support will be reviewed to determine if it is appropriate to ensure successful completion of the requested scope of the project.

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- o scientific merit (as determined by peer review)
- o availability of funds
- o programmatic priorities

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome. Direct inquiries regarding programmatic issues to:

Susana Serrate-Sztein, M.D.
Rheumatic Diseases Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A25
Bethesda Md 20892-6500
Telephone: (301) 594-5032
FAX (301) 480-4543
Email: szteins@mail.nih.gov

Direct review inquiries to:

Tommy Broadwater, Ph.D.
Review Branch,
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Natcher Bldg. Rm. 5A25U
Bethesda, MD 20892-6500
Telephone: (301) 594-4953
FAX (301) 480-4543

Email: broadwatert@mail.nih.gov

Direct inquiries regarding fiscal matters to:

Melinda Nelson

Grants Management Officer

National Institute of Arthritis and Musculoskeletal and Skin Diseases

45 Center Drive, Natcher Bldg. Rm. 5A49

Bethesda Md 20892-6500

Telephone: (301) 594-3535

FAX (301) 480-5450

Email: mn23z@nih.gov

Schedule:

Letter of Intent Receipt Date: October 1, 2000

Application Receipt Date: December 15, 2000

Peer Review Date: March 2001

Council Review: June 2001

Earliest Anticipated Start Date: July 2001

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846, Arthritis, Musculoskeletal and Skin Diseases Research. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The Public Health Service strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or, in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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